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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/405,454	03/15/95	SULLIVAN J	4249.0002-05

EXAMINER	
SCHWADRON	18N1/1127

ART UNIT	PAPER NUMBER
1816	17

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DATE MAILED: 11/27/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/5/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter. the office action mailed 10/31/95
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION: See paragraph 15 of previous office action

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 27, 29, 37-39 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 1-26, 30-36 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 27, 29, 37-39 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. The following supplemental Office Action is in response to the amendment received 10/5/95. The response date for this Office Action is the same as that for the Office Action mailed 10/31/95 because no new grounds of rejection are included in this Office Action. Claims 27,29,37-39 are under consideration. Claims 30-36 have been cancelled.

16. Applicants need to update the status of all US patent applications (eg. abandoned, etc.) disclosed in the specification (eg. 08/277,288 on page 1).

17. Claims 27,29,37-39 rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 39 is indefinite in that it lacks antecedent basis in claim 27. Claim 27 reads on a composition containing F(ab) fragments while claim 39 reads on an intact IgG(T)molecule which is not present in the F(ab) composition of claim 27. Claims 27 and 29 are indefinite in the recitation of a "composition comprising" because the additional ingredients which define a composition (eg. buffer, pharmaceutically acceptable carrier, etc.) are not recited in the claim. Claims 27 and 29 are indefinite in the recitation of "extraneous protein" because it is unclear what this means or encompasses. Claim 29 is indefinite in the recitation of "polyvalent F(ab) because it is unclear what this means or encompasses. F(ab) fragments are monovalent. It appears that applicants intend to refer to F(ab) fragments derived from polyvalent (eg. polyclonal) antisera. Applicants need to amend the claim using language supported in the specification.

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claim 29 is rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Coulter et al. as evidenced by Stedman's Medical Dictionary (1977).

Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). Stedman's Medical Dictionary defines antivenin as "an antitoxin specific for an animal or insect toxin"(page 94). Therefore the composition taught by Coulter et al. is an antivenin. The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract).

20. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

21. Claims 27,29,37-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan et al. in view of Coulter et al. and Smith et al. as evidenced by Stedman's Medical Dictionary (1977).

The claims are drawn to antivenin compositions consisting of F(ab) fragments. Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus (see *Methods* section, pages 185-187). These antibodies are predominantly IgG(T), because that is the predominant isotype found in hyperimmune horse antisera. A routineer would have used the procedure of Sullivan et al. to produce purified antivenin antibodies against any desired venom. A routineer would have immunized horses to produce said hyperimmune antisera because this is the art recognized procedure for producing antivenin. Sullivan et al. do not teach a F(ab) containing antivenin.

Coulter et al. teaches a method for producing F(ab) fragments that are free of Fc (see abstract). Coulter et al. teaches a composition of F(ab) fragments of antibody against textilotoxin (a snake toxin) (see pages 201-203). Stedman's Medical Dictionary defines antivenin as "an antitoxin specific for an animal or insect toxin"(page 94). Therefore the composition taught by Coulter et al. is an antivenin. The F(ab) composition (page 201, third paragraph) was derived from polyclonal antisera against textilotoxin (page 199, second paragraph). The F(ab) produced by said method were free of Fc and extraneous protein (see Abstract). A routineer would have

assayed for Fc by immunoelectrophoresis using anti-Fc antibodies or any other art recognized procedure.

Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications (see page 393, first paragraph, *Discussion* section). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced antivenin compositions consisting of F(ab) fragments because Sullivan et al. teach purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus, a routineer would have used the procedure of Sullivan et al. to produce purified antivenin antibodies against any desired venom, Coulter et al. teaches a method for producing antivenin F(ab) fragments that are free of Fc, and Smith et al. teaches the advantages of F(ab) fragments for the neutralization and clearance of toxic substances in therapeutic applications. One of ordinary skill in the art would have been motivated to do the aforementioned because Smith et al. teaches that,

"Relatively rapid clearance of Fab fragments can be used to advantage when the objective is rapid neutralization and clearance of a toxic substance, and purified sheep digoxin specific Fab fragments have been utilized clinically for the reversal of advanced digoxin intoxication. This therapeutic approach is based on similar binding properties and the postulated lesser immunogenicity of Fab compared with IgG. For urgent clinical situations such as life threatening digitalis-toxic cardiac arrhythmias, the present study indicates that Fab has another important advantage-more rapid and extensive distribution to its presumed site of action in the interstitial space." (page 393). Further motivation is provided by the teaching of Coulter et al. that F(ab) antivenin can be made and that said antivenin work in vivo to neutralize snake toxins (see page 202, third paragraph). In

addition, Sullivan et al. teach that reducing the immunogenicity of polyvalent horse antivenin is an important goal, due to immune reactions that limit the clinical efficacy of antivenin preparations which contain only partially purified hyperimmune horse antisera (see page 185, first paragraph).

Applicants arguments in the amendment received 1/17/95 have been considered and deemed not persuasive. Regarding the various hypothetical scenarios in the Smith declaration (pages 2 and 3) as to why F(ab) fragments would not be expected to neutralize snake venom in vivo (which are repeated in pages 4-9 of the amendment received 1/17/95), Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo as effectively as IgG (see page 202, third paragraph). With regards to the clinical study depicted in paragraphs 12 and 13 of the Smith declaration, there is no disclosure in the specification of TAb001, or a F(ab) fragment containing antisera against Vipera berus. Regarding applicants comments about on page 7 of the amendment received 1/17/95, neither F(ab) or intact IgG have any effect on alpha-amanitin poisoning, so that this point is irrelevant to the discussion at hand. Regarding applicants comments on page 8, Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo as effectively as IgG (see page 202, third paragraph). Regarding the alleged unexpected results disclosed in the Smith declaration (page 9-10 of the amendment received 1/17/95), there is no disclosure in the specification of TAb001, or a F(ab) fragment containing antisera against Vipera berus. Regarding applicants comments about nonobviousness and long-felt need, Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo as effectively as IgG (see page 202, third paragraph).

Regarding applicants comments in the amendment received 10/5/95, applicants arguments have been considered and deemed not persuasive. Regarding applicants comments about unexpected

results, nonobviousness and long-felt need, Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo (see page 202, third paragraph). Regarding applicants comments about the Smith et al. declaration, none of the claims under consideration are drawn to TAbool, the antibody preparation disclosed in said declaration. In addition, TAb001 is an ovine antibody preparation which is not disclosed in the instant application. Regarding the Smith declaration, Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo (see page 202, third paragraph). Regarding applicants comments about Sorkine et al., Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo (see page 202, third paragraph). Regarding applicants comments about Laing et al., Coulter et al. teaches that F(ab) antivenin can neutralize snake toxin in vivo (see page 202, third paragraph). Regarding applicants comments about clinical efficacy of antivenins in humans, the claims are drawn to a composition which could be used as an antivenin to treat animals. Applicant is also reminded that the recitation of an intended use in a product claim carries no patentable weight.

22. Papers related to this application may be submitted to Group 180 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Group 180 at (703) 305-7401.

23. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Dr. Ron Schwadron whose telephone number is (703) 308-4680. The examiner can normally be reached Tuesday through Friday from 8:30 to 6:00. The examiner can also be reached on alternative Mondays. A message may be left on the examiners voice mail service. If attempts to

reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ms Margaret Moskowitz Parr can be reached on (703) 308-2454. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

R Schwadron

Ron Schwadron, Ph.D.
Patent Examiner
Art Unit 1806
November 22, 1995

MARGARET PARR
SUPERVISOR PATENT EXAMINER
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